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(19) (CA) **CANADIAN PATENT** (12)

(54) Terra-Substituted Benzene Derivatives

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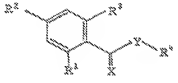
ABSTRACT

Novel compounds of the general formula



I

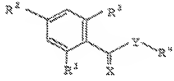
wherein X represents an oxygen or sulphur atom or hydroxyimino; Y represents methylene or imino; R^1 represents a hydroxy, phosphonooxy, glycosyloxy, acylated glycosyloxy, acyloxy or lower alkoxycarbonyloxy; R^2 represents lower alkoxy, lower alkenyloxy or lower alkylthio; R^3 represents lower alkoxy; R^4 represents lower alkyl, p-lower-alkoxy-benzoyl or a substituted or unsubstituted phenyl, benzyl, pyridylmethyl, furfuryl, tetrahydrofurfuryl, thenyl tetrahydrothenyl, pyrrolylmethyl, pyrrolinylmethyl or pyrrolidinylmethyl group, with the proviso that when R^4 represents alkyl, a phenyl including lower alkyloxy phenyl, benzyl or p-hydroxybenzyl, Y does not represent a methylene radical; and with the further proviso that when R^4 represents p-methoxybenzyl and Y represents methylene, R^2 and R^3 are different,

and pharmaceutically acceptable salts thereof, possess antiviral activity. The compounds of formula I can be prepared by various methods.

B

The present invention relates to novel tetra-substituted benzene compounds, a process for the preparation thereof and antiviral agents containing same.

More particularly, the present invention relates to novel tetra-substituted benzens compounds of the general foxmula



I

wherein X represents an oxygen or sulphur atom or hydroxyimino; Y represents methylene or imino; R^1 represents a hydroxy, phosphonooxy, glycosyloxy, acylated glycosyloxy, acyloxy or lower alkoxycarbonyl-oxy; R^2 represents lower alkoxy, lower alkenyloxy or lower alkylthio; R^3 represents lower alkoxy; R^4 represents lower alkyl, p-lower-alkoxy-benzoyl or a phenyl, benzyl, pyridylmethyl, furfuryl, tetrahydrofurfuryl, thenyl, tetrahydrothenyl, pyrrolylmethyl, pyrrolinylmethyl or pyrrolidinylmethyl group, with the proviso that when R^4 represents alkyl, a phenyl, benzyl or p-hydroxybenzyl, Y does not represent a

methylene radical; and with the further proviso that when R^4 represents p-methoxybenzyl and Y represents methylene, R^2 and R^3 are different,

and pharmaceutically acceptable salts thereof.

Preferred examples of glycosyloxy and acylated glycosyloxy are β-D-glucopyranosyloxy and tetra-O-acetyl-β-D-glucopyranosyloxy. The acyloxy radicals are preferably derived from aliphatic acids containing from 2 to 18 carbon atoms or from aromatic acids, preferred acyloxy radicals being acetoxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, stearoyloxy and benzoyloxy. The lower alkoxycarbonyloxy radicals contain preferably up to 7 carbon atoms, a preferred alkoxycarbonyloxy radical being ethoxycarbonyloxy. The lower alkoxy radicals contain preferably from 1 to 6 carbon atoms, especially from 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy or butoxy. The lower alkylthio radicals contain preferably 1 to 6 carbon atoms especially from 1 to 4 carbon atoms, such as methylthio. The lower alkyl radicals contain preferably from 1 to 6 carbon atoms, especially from 1 to 4 carbon atoms, such as methyl, ethyl, propyl and butyl. The lower alkenyloxy radicals contain preferably from 2 to 7 carbon atoms, especially from 2 to 4 carbon atoms, such as allyloxy and 3-methyl-2-propenyloxy. Preferred examples of such phenyl, benzyl and pyridylmethyl radicals are phenyl, or lower alkoxy phenyl such as p-methoxyphenyl; benzyl which is substituted by

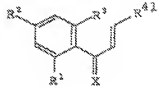
one or more substituents such as hydroxyl, halogen, lower alkyl, lower alkoxy, lower alkylthio, amino, dialkylamino, allyloxy, benzyloxy and alkylenedioxy, especially p-hydroxybenzyl, m-hydroxy-p-methoxybenzyl, p-chlorobenzyl, p-methylbenzyl, p-methoxybenzyl, m-methoxybenzyl, m,p-dimethoxybenzyl, p-butoxybenzyl, p-(methylthio)benzyl, p-(dimethylamino)-benzyl, p-(allyloxy)benzyl, p-(benzyloxy)benzyl, and m,p-(methylenedioxy)benzyl. An exemplary pyridylmethyl radical is 4-pyridylmethyl. Preferred examples of substituted furfuryl, thenyl and pyrrolylmethyl radicals and saturated derivatives thereof are furfuryl, 5-methylfurfuryl, tetrahydro-5-methylfurfuryl, 2-thenyl, tetrahydro-2-thenyl, and 2-pyrrolylmethyl.

A preferred group of compounds of formula I are those wherein R^2 is lower alkoxy or lower alkylthio and R^1, R^3, R^4, X and Y are as defined above.

Also preferred are compounds of formula I wherein R^1 is hydroxy, lower alkanoyloxy, benzoyloxy, phosphonooxy, lower alkoxycarbonyloxy; R^2 is lower alkoxy or lower alkenyloxy; R^3 is lower alkoxy; R^4 is substituted phenyl; and X is a oxygen or sulfur atom and Y is methylene or imino, especially those wherein Y is imino. Compounds of particular interest are 4-ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)-benzamide, 2-[(p-anisylamino)carbonyl]-5-ethoxy-3-methoxyphenyl dihydrogen phosphate and the disodium salt thereof.

According to the process provided by the present invention, the novel tetra-substituted benzene compounds of formula I and their pharmaceutically acceptable salts are prepared by

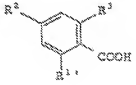
(a) hydrogenating a compound of the general formula



II

wherein X, R^1, R^2, R^3 are as defined in formula I, and R^{41} represents pyridyl, furyl, terrahydrofuryl, thianyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl or pyrrolidinyl, in the presence of a catalyst in a solvent, or

(b) reacting a reactive derivative of a carboxylic acid of the general formula



III

wherein R^2 and R^3 are as defined in formula I and $R^{1'}$ represents a protected hydroxyl radical,

with a compound of the general formula

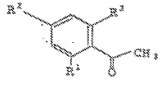
$$R^4 - NH_2 \qquad IV$$

wherein R^4 is as defined in formula I,

and then removing the protecting moiety of the protected hydroxyl radical,

or

(c) reacting an acetophenone of the general formula



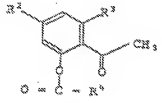
V

wherein R^1, R^2 and R^3 are as defined in formula I,

with iodine in a tertiary amine and reacting a resulting salt with an amine of formula IV hereinbefore,

or

(d) subjecting an ester of the general formula



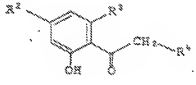
VI

wherein R^2, R^3 and R^4 are as defined in formula I,

to rearrangement in the presence of a base in a solvent,

or

(e) reacting a ketone of the general formula



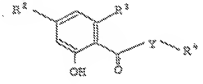
VII

wherein R^2, R^3 and R^4 are as defined in formula I,

with a salt of hydroxylamine in a solvent,

or

(f) reacting a carbonyl compound of the general formula



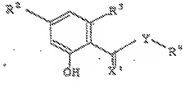
VIII

wherein Y, R^2, R^3 and R^4 are as defined in formula I,

with phosphorus pentasulphide in the presence of a base in a solvent,

or

(g) reacting a phenol of the general formula



IX

wherein Y, R^2, R^3 and R^4 are as defined in formula I and X' represents an oxygen or sulphur atom,

with an acylating agent in the presence of a base,

or

(h) reacting a phenol of formula IX hereinbefore with phosphorus oxychloride or dibenzylphosphorochloridate in the presence of a base in a solvent followed by hydrolysis or hydrogenolysis as the case may require and, if necessary, converting a resulting compound into a salt,

or

(i) reacting a phenol of formula IX hereinbefore with a glycosyl halide which may be acylated in the presence of a catalyst in a solvent, followed, if necessary, by removal of the acyl radicals.

The hydrogenation in accordance with embodiment (a) of the process can be carried out by treating a compound of formula II with hydrogen in the presence of a catalyst such as palladium black, palladium-on-charcoal and the like in a solvent such as chloroform.

The reaction in accordance with embodiment (b) of the process can be effected by reacting a reactive derivative of a carboxylic acid of formula III with an amine of formula (IV) followed by removal of the protecting moiety of the protected hydroxyl radical in the resulting compound. Preferred examples of such reactive derivatives of carboxylic acids of formula III are acyl halides such as acyl chlorides, acyl bromides and the like and active esters such as the N-hydroxysuccinimide ester, p-nitrophenyl ester and the like. The removal of the protecting moiety of the protected hydroxyl radical can be performed by a method known per se.

The reaction in accordance with embodiment (c) of the process is a novel reaction. In carrying out this reaction, an acetophenone of formula V is reacted with iodine in a tertiary amine such as pyridine, lutidine or the like at an elevated temperature and subsequently a resulting salt is reacted with an amine of formula IV.

The base-catalized rearrangement in accordance with embodiment (d) of the process can be carried out by subjecting an ester of formula VI to rearrangement in the presence of a base such as potassium carbonate, sodium hydride, sodium amide or the like in a solvent such as benzene, toluene, tetrahydrofuran, dioxan or the like.

The oximation in accordance with embodiment (e) of the process can be effected by reacting a ketone of formula VII with a salt of hydroxylamine in a solvent such as dimethyl sulphoxide.

The reaction in accordance with embodiment (f) of the process can be carried out by reacting a carbonyl compound of formula VIII with phosphorus pentasulphide in the presence of a base such as triethylamine in a solvent such as carbon disulphide.

The acylation of the hydroxyl radical in a phenol of formula IX in accordance with embodiment (g) of the

process can be carried out in a manner known per se by treatment with an acylating agent such as acetic anhydride, ethoxycarbonyl chloride, stearic anhydride, benzoyl chloride or the like in the presence of a base such as sodium acetate, pyridine, triethylamine, 4-(dimethylamino)pyridine or the like.

The phosphorylation of the hydroxyl radical in a phenol of formula IX in accordance with embodiment (h) of the process can be effected in a manner known per se by treatment with phosphorus oxychloride or dibenzylphosphorochloridate in the presence of a base such as triethylamine, N,N-diisopropylamine or the like in a solvent such as benzene, toluene, triethylamine or the like. When phosphorus oxychloride is used, the resulting compound is hydrolyzed. When dibenzylphosphorochloridate is used, the resulting compound is subject to hydrogenolysis. The phosphate of a compound of formula IX thus obtained may be converted into a salt by a process known per se.

The glycosidation of the hydroxyl radical in a phenol of formula IX in accordance with embodiment (i) of the process can be carried out in a manner known per se by treatment with a glycosyl halide in which the hydroxyl radicals are protected by protecting radicals such as acetyl, benzyl and the like. Preferred glycosyls are glucosyl, mannosyl, glucosaminyl and the like.

The compounds of formula I provided by the present invention exhibit an antiviral activity and, in particular, inhibit the replication of human rhinoviruses in Hela cell culture at 0.001 to 2.7 µg/ml.

The present invention also relates to antiviral agents containing a compound of formula I or a pharmaceutically acceptable salt thereof. The compounds of formula I are particularly effective against certain viruses of the Picorna group. However, the following compounds have particularly strong antiviral activity:

1-(4-Ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone,

5-ethoxy-3-methoxy-2-[3-(p-methoxyphenyl)-propionyl]phenyl acetate,

4-ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide,

2-hydroxy-4,6-dimethoxy-N-[p-(methylthio)benzyl]-benzamide,

2-{[[p-(allyloxy)benzyl]amino]carbonyl}-3,5-dimethoxyphenyl benzoate,

1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanethione,

5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)-propionyl]phenyl ethyl carbonate,

2-[(p-anisylamino)carbonyl]-5-ethoxy-3-methoxyphenyl dihydrogen phosphate,

disodium 2-[(p-anisylamino)carbonyl]-5-ethoxy-3-methoxyphenyl phosphate,

2-hydroxy-6-methoxy-4-propoxy-N-(p-methoxybenzyl)benzamide,

4-(allyloxy)-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide,

2-hydroxy-6-methoxy-4-(3-methyl-2-butenyloxy)-N-(p-methoxybenzyl)benzamide and

disodium 2-[(p-anisylamino)carbonyl]-3-methoxy-5-propoxyphenyl phosphate.

Antiviral Activity

A suspension of HeLa cells (6×10^4) was mixed with rhinovirus HGP (3×10^3 plaque-forming units, PFU) and was plated in a microtest plate containing the compounds to be tested serially diluted. The cells were then cultured with Eagle's minimum essential medium containing 2% calf serum, 1% tryptose phosphate broth, 100 µg/ml of streptomycin and 20 units/ml of penicillin G. The viral C.P.E. (cytopathogenic effect) and cytotoxicity were observed by a microscope after 2 days culture at 33°C. The antiviral activity (IC_{50}) of the test compounds is expressed by the concentration inhibiting the viral C.P.E. by 50% when compared with the control culture. The cytotoxicity is expressed as the minimum concentration at which toxic symptoms were observed (cytotoxic dose).

The results are shown in Table 1 and demonstrate

that the compounds provided by the present invention exhibit anti-rhinovirus activity at concentrations which are 10 to 10,000 times lower than their cytotoxic doses.

In addition, the antiviral spectra of 1-(4--ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)--1-propanone (compound A) and 4-ethoxy-2-hydroxy-6--methoxy-N-(p-methoxybenzyl)benzamide (compound B) against various serotypes of rhinovirus are shown in Table 2.

Table 1

Compound	IC_{50} (μg/ml)	Cytotoxicity (μg/ml)
1-(2-Hydroxy-4,6-dimethoxy-phenyl)-3-[3,4-(methylene-dioxy)phenyl]-1-propanone	0.03 - 0.1	>8
1-(2-Hydroxy-4,6-dimethoxy-phenyl)-3-[4-methylthio)-phenyl]-1-propanone	0.01 - 0.03	8
1-(2-Hydroxy-4,6-dimethoxy-phenyl)-3-(4-methylphenyl)--1-propanone	0.01 - 0.03	>8
1-(4-Ethoxy-2-hydroxy-6--methoxyphenyl)-3-(4--methoxyphenyl)-1-propanone	0.002	>8
5-Ethoxy-3-methoxy-2-[3-(p--methoxyphenyl)propionyl]-phenyl dihydrogen phosphate	0.3 - 0.8	>10
5-Ethoxy-3-methoxy-2-[3-(p--methoxyphenyl)propionyl]-phenyl acetate	0.001	>8
1-(2-Hydroxy-4,6-dimethoxy-phenyl)-3-(4-methoxyphenyl)--1-propanone oxime (Z-isomer)	0.03	>10
1-(2-Hydroxy-4,6-dimethoxy-phenyl)-3-(4-methoxyphenyl)--1-propanone oxime (E isomer)	0.3 - 0.9	>10
2-Hydroxy-4,6-dimethoxy--N-(p-methoxybenzyl)-benzamide	0.002	8
3-(4-Chlorophenyl)-1-(2--hydroxy-4,6-dimethoxy-phenyl)-1-propanone	0.1	10

Table 1 (continued)

Compound	IC_{50} (μg/ml)	Cytotoxicity (μg/ml)
1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(5-methyl-2-furyl)--1-propanone	0.9	>8
1-(2-Ethoxy-6-hydroxy-4--methoxyphenyl)-3-(4--methoxyphenyl)-1--propanone	0.01 - 0.03	0.9
1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)--1,3-propanedione	0.01 - 0.03	8
1-(2-Hydroxy-6-methoxy-4--propoxyphenyl)-3-(4--methoxyphenyl)-1--propanone	0.004 - 0.01	2.7
1-(2-Hydroxy-4-isopropoxy--6-methoxyphenyl)-3-(4--methoxyphenyl)-1-propanone	0.03 - 0.1	8
4-Ethoxy-2-hydroxy-6--methoxy-N-(p-methoxybenzyl)benzamide	0.002	>10
1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(tetrahydro-5--methyl-2-furyl)-1--propanone	0.9	>8
2-Hydroxy-4,6-dimethoxy-N--(4-methoxyphenyl)benzamide	0.03 - 0.1	>10
N-Benzyl-2-hydroxy-4,6--dimethoxybenzamide	0.03 - 0.1	>8

Table 1 (continued)

Compound	IC_{50} (µg/ml)	Cytotoxicity (µg/ml)
2-Hydroxy-4,6-dimethoxy-N-[m,p-(methylenedioxy)-benzyl]benzamide	0.003 - 0.01	>8
2-Hydroxy-4,6-dimethoxy-N-(m-methoxybenzyl)-benzamide	0.002	>8
2-Hydroxy-4,6-dimethoxy-N-(p-methylbenzyl)-benzamide	0.01 - 0.03	8
N-(p-Chlorobenzyl)-2-hydroxy-4,6-dimethoxy-benzamide	0.01 - 0.03	>2.4
N-Furfuryl-2-hydroxy-4,6-dimethoxybenzamide	0.03 - 0.1	>8
2-Hydroxy-4,6-dimethoxy-N-methylbenzamide	0.9	>8
2-Hydroxy-N-(m-hydroxy-p-methoxybenzyl)-4,6-dimethoxybenzamide	0.1 - 0.3	2.7
N-(m,p-Dimethoxybenzyl)-2-hydroxy-4,6-dimethoxy-benzamide	0.3	8
2-Hydroxy-4,6-dimethoxy-N-[(4-pyridyl)methyl]-benzamide	0.9	8

Table 1 (continued)

Compound	IC_{50} (μg/ml)	Cytotoxicity (μg/ml)
N-(p-Butoxybenzyl)-2-hydroxy-4,6-dimethoxybenzamide	0.3	8
2-Hydroxy-N-(p-hydroxybenzyl)-4,6-dimethoxybenzamide	0.3	>8
N-[p-Dimethylamino)benzyl]-2-hydroxy-4,6-dimethoxybenzamide	0.01	>8
2-Hydroxy-4,6-dimethoxy-N-[p-(methylthio)benzyl]-benzamide	0.002	>8
N-[p-(Benzyloxy)benzyl]-2-hydroxy-4,6-dimethoxybenzamide	0.3 - 0.9	>8
2-Hydroxy-4,5-dimethoxy-N-(2-thenyl)benzamide	0.03	8
N-[p-(Allyloxy)benzyl]-2-hydroxy-4,6-dimethoxybenzamide	0.01	8
2-Hydroxy-4,6-dimmathoxy-N-(tetrahydro-2-thenyl)-benzamide	0.004-0.01	8
2-Hydroxy-4,6-dimethoxy-N-[(2-pyrrolyl)methyl]-benzamide	2.7	>8

Table 1 (continued)

Compound	IC_{50} (µg/mℓ)	Cytotoxicity (µg/mℓ)
2-[(p-Anisylamino)-carbonyl]-5-ethoxy-3--methoxyphenyl acetate	0.3	>8
2-[[[p-(Allyloxy)benzyl]-amino]carbonyl]-3,5--dimethoxyphenyl benzoate	0.002	2.7
2-{[[p-(allyloxy)benzyl]-amino_/carbonyl}-3,5--dimethoxyphenyl octa-decanoate	0.3	>8
1-(4-Ethoxy-2-hydroxy-6--methoxyphenyl)-3-(4-methoxy-phenyl)-1-propanethione	0.002	2.7
4-Ethoxy-2-hydroxy-6-methoxy--N-(p-methoxybenzyl)thio-benzamide	0.01	>8
1-[2-Hydroxy-6-methoxy-4--(methylthio)phenyl]-3--(4-methoxyphenyl)-1--propanone	0.1	1
5-Ethoxy-3-methoxy-2-[3-(4--methoxyphenyl)propionyl]-phenyl ethyl carbonate	0.002	8
5-Ethoxy-3-methoxy-2-[3-(4--methoxyphenyl)propionyl]-phenyl octadecanoate	0.9	>8

Table 1 (continued)

Compound	IC_{50} (μg/mℓ)	Cytotoxicity (μg/mℓ)
5-Ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)-propionyl]phenyl benzoate	0.01	>8
2-[(p-Anisylamino)carbonyl]-3,5-dimethoxyphenyl ethyl carbonate	0.1	>8
2-[(p-Anisylamino)carbonyl]-3,5-dimethoxyphenyl benzoate	0.03	>8
2-[(p-Anisylamino)carbonyl]-3,5-dimethoxyphenyl octadecanoate	0.3 ~ 0.9	>8
2-[(p-Anisylamino)carbonyl]-3,5-dimethoxyphenyl tetra-O-acetyl β-D-glucopyranoside	2.7	>10
2-[(p-Anisylamino)carbonyl]-3,5-dimethoxyphenyl β-D-glucopyranoside	2.7	>10
5-Ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)propionyl]-phenyl β-D-glucopyranoside	2.7	>10
Disodium 5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)-propionyl]phenyl phosphate	0.03 ~ 0.1	>10

Table 1 (continued)

Compound	IC_{50} (μg/ml)	Cytotoxicity (μg/ml)
2-[(p-Anisylamino)carbonyl]-3,5-dimethoxyphenyl dihydrogen phosphate	0.006-0.01	>8
2-[(p-Anisylamino)carbonyl]-5-ethoxy-3-methoxyphenyl dihydrogen phosphate	0.01 -0.03	>8
Disodium 2-[(p-anisylamino)-carbonyl]-5-ethoxy-3-methoxyphenyl phosphate	0.01 -0.03	>8
2-Hydroxy-6-methoxy-4-propoxy-N-(p-methoxybenzyl)benzamide	0.001-0.003	>20
4-(Allyloxy)-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide	0.002	>8
2-Hydroxy-6-methoxy-4-[3-methyl-2-butenyloxy)-N-(p-methoxybenzyl)-benzamide	0.001-0.002	>8
Disodium 2-[(p-anisylamino)-carbonyl]-3-methoxy-5-propoxyphenyl phosphate	0.01 -0.02	>200

Table 2

Virus Strain	IC_{50} (μg/mℓ)	
	Compound A	Compound B
Rhinovirus 1A	0.03 - 0.09	0.009 - 0.027
1B	0.03 - 0.09	0.003 - 0.009
2	0.001	0.001
9	0.012 - 0.037	0.003
14	0.1 - 0.3	0.009 - 0.027
16	-	0.003
21	<0.001	<0.001
23	0.004	-
24	0.01 - 0.03	-
25	0.01 - 0.09	-
30	-	0.001 - 0.003
31	0.03 - 0.09	0.081 - 0.24
32	-	0.003 - 0.009
36	-	0.009 - 0.027
39	0.012 - 0.037	0.003
44	-	0.003
46	0.037 - 0.11	-
47	-	0.003
50	0.004 - 0.012	0.01
55	-	0.009

Cytotoxic doses inhibiting HeLa cells growth by 50% are 80 μg/mℓ (A) and 40 μg/mℓ (B), respectively.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable salts can be used as medicaments against viral diseases, especially in the common cold, in the form of pharmaceutical preparations.

The pharmaceutical preparations contain at least one of said antiviral compounds or pharmaceutically acceptable salts thereof in association with a compatible pharmaceutical carrier material and they may also contain other pharmaceutically active compounds such as a febrifuge, an anodyne, an anti-inflammatory, an anti-histamine, an interferon-inducer or the like. The pharmaceutical preparations include solid forms for oral administration such as tablets, capsules, pills, powders or granules, liquid forms for nasal or oral administration such as solutions, suspensions, syrups or elixers, forms for parenteral administration such as sterile solutions, suspensions or emulsions and forms for topical administration such as solutions, emulsions, micronized powders, ointments, gargles, troches or aerosols.

The pharmaceutical preparations can be administered so that the concentration of active ingredient is greater than the minimum inhibitory concentration for the particular viral infection being treated.

The dosage for treatment depends on the route of administration, the age, weight and condition of the patient and the particular disease to be treated. In general, for adults a suggested dosage for use in the common cold is about 100 to 2,000 mg three to six times daily in the case of oral treatment and about 0.1 to 100 $\mu g/cm^2$ three to six times daily in the case of topical administration.

The following Examples illustrate the present invention:

Example 1

A solution of 328 mg of 4'-ethoxy-2'-hydroxy-4,6'-dimethoxychalcone in 10 ml of chloroform was hydrogenated in the presence of 30 mg of 10% palladium-on-charcoal at room temperature under atmospheric pressure for 3 hours. The catalyst was removed by filtration and washed with 30 ml of chloroform. The filtrate and the washing were combined and evaporated under reduced pressure to give a crystalline residue. Recrystallization of the residue from methanol yielded 302 mg of 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone as colourless needles of melting point 100.5° - 101°C.

Example 2

In a manner analogous to that described in Example 1, the products listed in Table 3 were obtained from the corresponding chalcones listed in Table 3.

Table 3

Chalcones	Products
2'-Hydroxy-4,4',6'-trimethoxychalcone	1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-1-propanone; melting point 110°C (recrystallized from methanol)
2'-Hydroxy-4'-6'-dimethoxy-4-(methylthio)-chalcone	1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-[4-(methylthio)-phenyl]-1-propanone; melting point 84° - 85°C (methanol)
2'-Hydroxy-4',6'-dimethoxy-3,4-(methylenedioxy)-chalcone	1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-[3,4-(methylenedioxy)-phenyl]-1-propanone; melting point 124.5°C (methanol)
2'-Hydroxy-4',6'-dimethoxy-4-methylchalcone	1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methylphenyl)-1-propanone; melting point 128° - 129°C (methanol)
4-Chloro-2'-hydroxy-4',6'-dimethoxychalcone	3-(4-Chlorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)-1-propanone; melting point 104.5°C (benzene/hexane)
2'-Ethoxy-6'-hydroxy-4,4'-dimethoxychalcone	1-(2-Ethoxy-6-hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone; melting point 108° - 109°C (benzene/hexane)

Example 3

A solution of 400 mg of 2'-hydroxy-4',6'-dimethoxy--3-(5-methyl-2-furyl)acrylophenone in 25 ml of chloroform was hydrogenated in the presence of 40 mg of 10% palladium-on-charcoal at room temperature under atmospheric pressure for 4 hours. After removal of the catalyst by filtration, the filtrate was evaporated to give an oily residue which was dissolved in a small amount of benzene. The solution was applied to a column of silica gel and the column was eluted with hexane/ethyl acetate (5:1, v/v), giving two fractions, A (Rf 0.29) and B (Rf 0.16), when monitored by silica gel thin-layer chromatography using cyclohexane/ethyl acetate (4:1, v/v). Removal of the solvent from fraction A and recrystallization from benzene/hexane gave 192 mg of 1-(2-hydroxy-4,6--dimethoxyphenyl)-3-(5-methyl-2-furyl)-1-propanone as colourless crystals of melting point 92° - 93°C.

Similar working-up of fraction B gave 25 mg of 1-(2-hydroxy-4,6-dimethoxyphenyl)-3-(tetrahydro-5--methyl-2-furyl)-1-propanone as colourless needles of

melting point 67.5°C (recrystallized from petroleum ether).

Example 4

85 mg of 2'-hydroxy-4,6'-dimethoxy-4'-propoxychalcone were hydrogenated in a manner analogous to that described in Example 1. There were obtained 69 mg of 1-(2-hydroxy-6-methoxy-4-propoxyphenyl)-3-(4-methoxyphenyl)-1-propanone as colourless needles of melting point 85° - 86°C.

The 2'-hydroxy-4,6'-dimethoxy-4'-propoxychalcone used as the starting material was prepared as follows:

A mixture of 182 mg of 2', 4'-dihydroxy-6'-methoxyacetophenone, 187 mg of propyl iodide and 276 mg of anhydrous potassium carbonate in 5 ml of acetone was heated under reflux for 16 hours. After cooling, the mixture was diluted with 30 ml of water and extracted three times with 30 ml of dichloromethane each time.

The combined dichloromethane extracts were washed with water, dried over sodium sulphate and evaporated to give crude 2'-hydroxy-6'-methoxy-4'-propoxyacetophenone as a pale yellow oil.

The foregoing oil was dissolved in 5 ml of ethanol containing 120 mg of p-methoxybenzaldehyde, to which 4 ml of 15% aqueous sodium hydroxide were added. After stirring at room temperature for 2 days, the mixture was adjusted to pH 5 - 6 with hydrochloric acid and extracted with three 30 ml portions of ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over sodium sulphate and evaporated to give an oily residue. Recrystallization of the residue from methanol gave 110 mg of 2'-hydroxy-4,6'-dimethoxy-4'-propoxy-chalcone as yellow needles of melting point 95° - 96°C.

Example 5

In a manner analogous to that described in Example 1, from 2'-hydroxy-4'-isopropoxy-4,6'-dimethoxychalcone there was obtained 1-(2-hydroxy-4-isopropoxy-6-methoxy-phenyl)-3-(4-methoxyphenyl)-1-propanone of melting point 96.5°C (recrystallized from methanol).

The starting material was prepared in a manner analogous to that described in Example 4, except that isopropyl iodide was used instead of propyl iodide.

Example 6

120 mg of 2'-hydroxy-4,6'-dimethoxy-4'-(methylthio)-chalcone were dissolved in 10 ml of chloroform. The solution was hydrogenated in the presence of 180 mg of 10% palladium-on-charcoal at room temperature under atmospheric pressure for 33 hours. After removal of the catalyst by filtration, the filtrate was evaporated to give a pale yellow residue which was recrystallized from methanol. There were obtained 103 mg of 1-[2-hydroxy-6-methoxy-4-(methylthio)phenyl]-3-(4-methoxyphenyl)-1-propanone as cream coloured needles of melting point 127° - 127.5°C.

The starting material was prepared as follows:

To a solution of 120 mg of 2'-hydroxy-5'-methoxy-

-4'-(methylthio)acetophenone and 92 mg of p-methoxybenzaldehyde in 6 ml of ethanol were added 4 ml of 15% aqueous sodium hydroxide. After stirring at room temperature for 24 hours, the mixture was diluted with 10 ml of water and acidified with 1N hydrochloric acid. The resulting crystalline precipitate was collected by filtration, washed with a small amount of 50% methanol and recrystallized from methanol to give 144 mg of 2'-hydroxy-4,6'-dimethoxy-4'-(methylthio)-chalcone as yellow needles of melting point 145° - 147°C.

Example 7

1 g of 2-(benzyloxy)-4,6-dimethoxybenzoic acid was dissolved in 5 ml of thionyl chloride and the solution was stirred at room temperature for 1 hour. Removal of excess thionyl chloride by repeated evaporation with the aid of benzene gave an oil which dissolved in 5 ml of benzene. The solution was added dropwise to an ice-cold solution of 1.8 ml of p-methoxybenzylamine in 5 ml of

benzene. After stirring at room temperature for 17 hours, the mixture was diluted with 50 ml of ethyl acetate, washed successively with dilute hydrochloric acid and water, dried over sodium sulphate and evaporated under reduced pressure to give 1.66 g of an oil.

The foregoing oil was dissolved in 2 ml of benzene and the solution was applied to a column of silica gel (60 g in hexane). The column was eluted with 600 ml of hexane/ethyl acetate (1:1, v/v). Removal of the solvent from the eluate followed by recrystallization from ethyl acetate gave 700 mg of 2-(benzyloxy)-4,6--dimethoxy-N-(p-methoxybenzyl)benzamide as colourless needles of melting point 123° - 124°C.

A solution of 700 mg of the foregoing benzamide in 20 ml of chloroform was hydrogenated for 4.5 hours in the presence of 140 mg of 10% palladium-on-charcoal at room temperature under atmospheric pressure. Removal of the catalyst by filtration followed by evaporation of the

filtrate gave a crystalline residue. Recrystallization of the residue from methanol yielded 475 mg of 2-hydroxy--4,6-dimethoxy-N-(p-methoxybenzyl)benzamide as colourless needles of melting point 108° - 109°C.

The 2-(benzoyloxy)-4,6-dimethoxybenzoic acid used as the starting material was prepared as follows:

To a stirred suspension of 39.75 g of methyl 2--hydroxy-4,6-dimethoxybenzoate and 207 g of anhydrous potassium carbonate in 2000 ml of acetone was added dropwise a solution of 22.3 ml of benzyl bromide in 300 ml of acetone. After stirring at room temperature for 78 hours, the mixture was filtered. The filtrate was evaporated under reduced pressure to give an oil which was dissolved in 500 ml of chloroform. The solution was washed with 400 ml of water, dried over sodium sulphate and evaporated to give 78.7 g of crude methyl 2-(benzyloxy)-4,6-dimethoxybenzoate as a colourless oil.

78.7 g of the foregoing crude ester were dissolved in 2200 ml of dioxan/methanol (4:1, v/v). To this solution were added 900 ml of 2.4N sodium hydroxide, the mixture was heated under reflux for 16 hours, cooled and then acidified with hydrochloric acid. The resulting crystalline precipitate was collected by filtration and washed with ethyl acetate to yield 48 g of 2-(benzyloxy)--4,6-dimethoxybenzoic acid as colourless needles of melting point 167° - 168°C.

Example 8

In a manner analogous to that described in Example 7, the products listed in Table 4 were obtained from 2--(benzyloxy)-4,6-dimethoxybenzoic acid (prepared as the starting material in Example 7) and the respective amines listed in Table 4.

Table 4

Amines	Products
p-Methoxyaniline	2-Hydroxy-4,6-dimethoxy-N-(4-methoxyphenyl)benzamide; melting point 131° - 132°C (recrystallized from methanol)
Benzylamine	N-Benzyl-2-hydroxy-4,6-dimethoxybenzamide; melting point 96°C (methanol)
m,p-(Methylenedioxy)-benzylamine	2-Hydroxy-4,6-dimethoxy-N-(m,p-methylenedioxybenzyl)benzamide; melting point 116° - 117°C (methanol)
m-Methoxybenzylamine	2-Hydroxy-4,6-dimethoxy-N-(m-methoxybenzyl)benzamide; melting point 95° - 96°C (methanol)
p-Methylbenzylamine	2-Hydroxy-4,6-dimethoxy-N-(p-methylbenzyl)benzamide; melting point 100° - 100.5°C (methanol)
p-Chlorobenzylamine	N-(p-Chlorobenzyl)-2-hydroxy-4,6-dimethoxybenzamide; melting point 131° - 132°C (methanol)
2-(Aminomethyl)furan	N-Furfuryl-2-hydroxy-4,6-dimethoxybenzamide; melting point 74° - 75°C (methanol)
Methylamine	2-Hydroxy-4,6-dimethoxy-N-methylbenzamide; melting point 144° - 145.5°C (methanol)

Table 4 (continued)

Amines	Products
m-(Benzyloxy)-p-methoxybenzylamine	2-Hydroxy-N-(m-hydroxy-p-methoxybenzyl)-4,6-dimethoxybenzamide; melting point 144° - 145°C (methanol)
m,p-Dimethoxybenzylamine	2-Hydroxy-4,6-dimethoxy-N-(m,p-dimethoxybenzyl)benzamide; melting point 115° - 116°C (methanol)
p-Butoxybenzylamine	N-(p-Butoxybenzyl)-2-hydroxy-4,6-dimethoxybenzamide; melting point 88° - 89°C (methanol)
p-Hydroxybenzylamine	2-Hydroxy-N-(p-hydroxybenzyl)-4,6-dimethoxybenzamide; melting point 170° - 171°C (methanol)
p-(Dimethylamino)-benzylamine	N-[p-(Dimethylamino)benzyl]-2-hydroxy-4,6-dimethoxybenzamide; melting point 79° - 82°C (methanol)
p-(Methylthio)-benzylamine	2-Hydroxy-4,6-dimethoxy-N-[p-(methylthio)bensyl]benzamide; melting point 119° - 120°C (methanol)
p-(Benzyloxy)-benzylamine	N-[p-(Benzyloxy)bensyl]-2-hydroxy-4,6-dimethoxybenzamide; melting point 109° - 110°C (methanol)
2-Thenylamine	2-Hydroxy-4,6-dimethoxy-N-(2-thenyl)benzamide; melting point 60°C (methanol)
Tetrahydro-2-thenylamine	2-Hydroxy-4,6-dimethoxy-N-(tetrahydro-2-thenyl)benzamide; melting point 81° - 82°C (methanol)

Example 9

To a cooled suspension of 2-(benzyloxy)-4,6-dimethoxybenzoic acid (1 g), prepared as the starting material in Example 7, and 400 mg of N-hydroxysuccinimide in 20 ml of dioxan were added 858 mg of dicyclohexylcarbodiimide. The mixture was stirred at room temperature for 19 hours and then filtered. Removal of the solvent from the filtrate gave an oil which was chromatographed on 50 g of silica gel eluting with hexane - ethyl acetate (4:1, v/v). The eluate was evaporated to give a syrup which upon standing in a cool place solidified as a crystalline mass.

225 mg of the solid obtained according to the preceding paragraph were dissolved in 5 ml of dimethylformamide. To the resulting solution were added 88 mg of p-methoxybenzylamine and the mixture was stirred at room temperature. After 18 hours, the mixture was diluted with 20 ml of 1N hydrochloric acid and extracted twice with 50 ml of ethyl acetate each time. The

combined ethyl acetate extracts were washed with water, dried over sodium sulphate and evaporated to give a crystalline residue. Recrystallization of the residue from ethyl acetate/hexane yielded 228 mg of 2-(benzyloxy)-4,6-dimethoxy-N-(p-methoxybenzyl)benzamide as colourless needles of melting point 123° - 124°C.

Removal of the benzyl group from the foregoing benzamide by hydrogenolysis following the procedure described in Example 7 yielded 2-hydroxy-4,6-dimethoxy-N-(p-methoxybenzyl)benzamide of melting point 108° - 109°C.

Example 10

To a solution of 980 mg of 2'-hydroxy-4',6'-dimethoxyacetophenone in 2 ml of pyridine were added 1.27 g of iodine. The mixture was heated at 100°C for 1 hour to give a solid mass. After cooling, the solid was washed successively with 50 ml of ether and a small amount of cold water and then dried under reduced pressure

to give 2 g of crude 1-[(2-hydroxy-4,6-dimethoxybensoyl)-methyl]pyridinium iodide as a brown powder.

1 g of the foregoing pyridinium salt was added to 514 mg of p-methoxybenzylamine and the mixture was heated at 80°C for 72 hours. After cooling, the mixture was poured into 20 ml of 1N hydrochloric acid. The resulting suspension was extracted twice with 100 ml of dichloromethane each time. The combined dichloromethane extracts were washed with water, dried over sodium sulphate and evaporated to give 945 mg of an oily residue which was purified by silica gel chromatography using hexane/ethyl acetate (3:1, v/v) for the elution. Removal of the solvent from the eluate followed by recrystallization of the residue from methanol gave 316 mg of 2-hydroxy-4,6-dimethoxy-N-(p-methoxybenzyl)-benzamide of melting point 108° - 109°C.

Example 11

In a manner analogous to that described in Example 10, the products listed in Table 5 were obtained from the

pyridinium salt prepared in Example 10 and the respective amines listed in Table 5.

Table 5

Amines	Products
4-(Aminomethyl)pyridine	2-Hydroxy-4,6-dimethoxy-N-[(4-pyridyl)methyl]benzamide; melting point 114° - 115°C (recrystallized from ether)
p-(Allyloxy)benzylamine	N-[p-(Allyloxy)benzyl]-2-hydroxy-4,6-dimethoxybenzamide; melting point 93° - 94°C (methanol)
2-(Aminomethyl)pyrrole	2-Hydroxy-4,6-dimethoxy-N-(2-pyrrolylmethyl)benzamide; melting point 116° - 117°C (ether)

Example 12

A solution of 9.8 g of 4'-ethoxy-2'-hydroxy-6'-methoxyacetophenone and 12 g of iodine in 22 ml of pyridine was heated at 100°C for 1 hour. The resulting

slurry was cooled, triturated and again heated at 100°C for 1 hour. After cooling, the mixture was filtered and the solid residue was washed successively with 100 ml of ether and 100 ml of water and then dried at 60°C for 3 hours under reduced pressure. There were obtained 18.2 g of 1-[(4-ethoxy-2-hydroxy-6-methoxybenzoyl)methyl] pyridinium iodide as a pale brown solid.

15.4 g of the foregoing pyridinium salt were added to 10 ml of p-methoxybenzylamine and the stirred mixture was heated at 80°C for 18 hours under nitrogen. After cooling, the mixture was treated with 200 ml of ethyl acetate and 150 ml of water. The ethyl acetate phase was separated and the aqueous phase was extracted with 150 ml of ethyl acetate. The combined ethyl acetate solutions were washed successively with two 150 ml portions of dilute hydrochloric acid, 150 ml of aqueous sodium bicarbonate and brine, dried over sodium sulphate and then evaporated to give 15 g of an oil which was purified by silica gel chromatography using hexane/ethyl acetate for the elution. Removal of the solvent from the eluate

followed by recrystallization of the residue from methanol yielded 6.3 g of 4-ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide as colourless needles of melting point 87° - 88°C.

Example 13

A mixture of 336 mg of 2-acetyl-3,5-dimethoxyphenyl-4-methoxybenzoate and 735 mg of anhydrous potassium carbonate in 5 ml of toluene was heated at 100°C for 17 hours, cooled and then filtered. After washing with benzene, the filtered cake was treated with 50 ml of dichloromethane and 50 ml of water. The dichloromethane phase was separated, dried over sodium sulphate and evaporated to give a crystalline residue. Recrystallization of the residue from methanol gave 77 mg of 1-(2-hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-1,3-propanedione as yellow prisms of melting point 136° - 136.5°C.

Example 14

To a stirred suspension of 580 mg of 1-(2-hydroxy--4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-1-propanone, obtained as described in Example 2, and 482 mg of sodium acetate in 9 ml of dimethyl sulphoxide were added 204 mg of hydroxylamine hydrochloride. The mixture was heated at 80°C for 15.5 hours, cooled, diluted with 30 ml of ethyl acetate, washed successively with dilute hydrochloric acid and water, dried over sodium sulphate and then evaporated to give 710 mg of a yellow oil which was dissolved in 1 ml of benzene.

The solution obtained according to the preceding paragraph was applied to a column of 25 g of silica gel and the column was eluted with hexane/ethyl acetate (3:1, v/v) with fractionation (each fraction 15 ml). Fractions 5 to 8 were combined and evaporated to give 435 mg of a pale yellow oily residue. Recrystallization of the residue from ethyl acetate/hexane yielded 301 mg of the E isomer of 1-(2-hydroxy-4,6-dimethoxyphenyl)-3--(4-methoxyphenyl)-1-propanone oxime as colourless crystals of melting point 82° - 83.5°C.

The corresponding Z isomer of the oxime was also obtained as colourless crystals (melting point 102° - 104°C) from fractions 20 to 30 after removal of the solvent and subsequent recrystallization from ethyl acetate/hexane (yield 95 mg).

Example 15

A mixture of 500 mg of 4-ethoxy-2-hydroxy-6-methoxy--N-(p-methoxybenzyl)benzamide, obtained as described in Example 12, 673 mg of phosphorus pentasulphide and 259 mg of triethylamine in 10 ml of carbon disulphide was stirred at room temperature for 3 days. There were then added 100 ml of ethyl acetate and 100 ml of water and the mixture was shaken. The ethyl acetate phase was separated and the aqueous phase was extracted with 100 ml of ethyl acetate. The combined ethyl acetate solutions were washed with brine and evaporated. The residue was chromatographed on silica gel using benzene/ethyl acetate (10:1, v/v) for the elution. Removal of the solvent from the eluate and recrystallization from methanol yielded 4-ethoxy-2--hydroxy-6-methoxy-N-(p-methoxybenzyl)thiobenzamide as

pale yellow needles of melting point 98° - 99°C.

Example 16

In a manner analogous to that described in Example 15 but using 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone (obtained as described in Example 1) in place of 4-ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide, there was obtained 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanethione as orange needles of melting point 69° - 70°C (recrystallized from methanol).

Example 17

A mixture of 165 mg of 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone, 0.2 ml of acetic anhydride and 5 mg of sodium acetate in a sealed tube was heated at 140°C for 3 hours. After cooling, the mixture was poured into 20 ml of water. The mixture was extracted with 50 ml of chloroform and the extract was

washed with water, dried over sodium sulphate and evaporated to give 178 mg of an oily residue. Recrystallization of the residue from methanol gave 138 mg of 5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)-propionyl]phenyl acetate as colourless needles of melting point 58° - 59°C.

Example 18

To a solution of 200 mg of 4-ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide, obtained as described in Example 12, in 2 ml of pyridine was added 0.07 ml of acetic anhydride. The mixture was stirred at room temperature for 18 hours and then evaporated under reduced pressure to give an oily residue. Recrystallization of the residue from methanol gave 60 mg of 2-[(p-anisylamino)carbonyl]-5-ethoxy-3-methoxyphenyl acetate as colourless needles of melting point 121° - 122°C.

Example 19

To a solution of 317 mg of 2-hydroxy-4,6-dimethoxy--N-(p-methoxybenzyl)benzamide, obtained as described in Example 7, 0.14 ml of triethylamine and 24 mg of 4--(dimethylamino)pyridine in 20 ml of dichloromethane was added 0.1 ml of ethoxycarbonyl chloride. The mixture was stirred at room temperature for 1 hour, washed successively with dilute hydrochloric acid and water, dried over sodium sulphate and then evaporated to give 480 mg of a yellow oil. The oil was chromatographed on silica gel using hexane/ethyl acetate (3:1, v/v) for the elution. Removal of the solvent from the eluate and recrystallization from ether/petroleum ether gave 110 mg of 2-[(p-anisylamino)carbonyl]-3,5-dimethoxyphenyl ethyl carbonate as colourless crystals of melting point 123° - 124.5°C.

Example 20

In a manner analogous to that described in Example 19, but using 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3--(4-methoxyphenyl)-1-propanone in place of 2-hydroxy-4,6-

-dimethoxy-N-(p-methoxybenzyl)benzamide, there was obtained 5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)propionyl]-phenyl ethyl carbonate; ^{1}H-nmr spectrum (in $CDCl_3$): δ 1.38 (3H), 1.40 (3H), 3.00 (4H), 3.76 (6H), 4.02 (2H), 4.34 (2H), 6.32 (2H), 6.80 (2H) and 7.13 ppm (2H).

Example 21

To a solution of 200 mg of 2-hydroxy-4,6-dimethoxy-N-(p-methoxybenzyl)benzamide, obtained as described in Example 7, in 5 ml of pyridine were added 347 mg of stearic anhydride. The mixture was heated at 60°C for 22.5 hours and then evaporated under reduced pressure to give an oily residue which was dissolved in 30 ml of ethyl acetate. The solution was washed successively with dilute hydrochloric acid and brine, dried over sodium sulphate and evaporated. Recrystallization of the residue from ethyl acetate yielded 92 mg of 2-[(p-anisylamino)carbonyl]-3,5-dimethoxyphenyl octadecanoate as colourless needles of melting point 88° - 89°C.

Example 22

In a manner analogous to that described in Example 21, but using N-[p-(allyloxy)benzyl]-2-hydroxy--4,6-dimethoxybenzamide in place of 2-hydroxy-4,6--dimethoxy-N-(p-methoxybenzyl)benzamide, there was obtained 2-{[p-(allyloxy)benzyl]amino}carbonyl}-3,5--dimethoxyphenyl octadecanoate as colourless crystals of melting point 88° - 89°C (recrystallized from ethanol/hexane).

Example 23

In a manner analogous to that described in Example 21, but using 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone in place of 2-hydroxy-4,6-dimethoxy-N-(p-methoxybenzyl)benzamide, there was obtained 5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)propionyl]phenyl octadecanoate of melting point 40° - 41°C (recrystallized from methanol).

Example 24

In a manner analogous to that described in Example 19, but using benzoyl chloride in place of ethoxycarbonyl chloride, there was obtained 2-[(p-anisylamino)carbonyl]-3,5-dimethoxyphenyl benzoate as colourless crystals of melting point 124.5° - 125.5°C (recrystallized from ethyl acetate/hexane).

Example 25

In a manner analogous to that described in Example 19, but using N-[p-(allyloxy)benzyl]-2-hydroxy-4,6-dimethoxybenzamide (obtained as described in Example 11) and benzoyl chloride in place of 2-hydroxy-4,6-dimethoxy-N-(p-methoxybenzyl)benzamide and ethoxycarbonyl chloride, respectively, there was obtained 2-{[p-(allyloxy)benzyl]-amino}carbonyl}-3,5-dimethoxyphenyl benzoate as colourless crystals of melting point 105° - 106°C (recrystallized from methanol).

Example 26

In a manner analogous to that described in Example 19, but using 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone and benzoyl chloride in place of 2-hydroxy-4,6-dimethoxy-N-(p-methoxybenzyl)benzamide and ethoxycarbonyl chloride, respectively, there was obtained 5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)propionyl]phenyl benzoate; ^{1}H nmr spectrum: δ 1.42 (3H), 2.65 3.35 (4H), 3.75 (3H), 3.80 (3H), 4.06 (2H), 6.40 (2H), 6.75 (2H), 7.11 (2H) and 7.42 ~ 7.70 ppm (3H).

Example 27

To a solution of 990 mg of 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone, obtained as described in Example 1 and 2 ml of N,N-diisopropylethylamine in 20 ml of toluene were added in one portion 10 ml of phosphorus oxychloride. The

mixture was stirred at room temperature for 1.5 hours and then evaporated under reduced pressure at a bath temperature of below 40°C to give an oily residue which was dissolved in 10 ml of toluene. After removal of the solvent by evaporation under reduced pressure, the resulting oily residue was dissolved in 40 ml of tetrahydrofuran/water (1:3, v/v). The solution was vigorously stirred at room temperature for 50 minutes and concentrated under reduced pressure at a bath temperature of 30° - 40°C to an aqueous solution which was then extracted three times with 50 ml of chloroform each time. The combined chloroform extracts were washed with a small amount of water, dried over sodium sulphate and evaporated to give an oily residue which was dissolved in 100 ml of 0.1N potassium carbonate. The solution was washed twice with 30 ml of ethyl acetate each time, acidified with hydrochloric acid and extracted three times with 50 ml of ether each time. The combined ether extracts were washed with a small amount of water, dried over sodium sulphate and evaporated to give an oily residue. Recrystallization of the residue from ether

yielded 930 mg of 5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)propionyl]phenyl dihydrogen phosphate as colourless needles of melting point 122° - 125°C (decomposition).

Example 28

410 mg of 5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)-propionyl]phenyl dihydrogen phosphate, obtained as described in Example 27, were dissolved in 15 ml of 0.1N sodium hydroxide. After carefully adjusting the pH to 8.0 with 0.1N sodium hydroxide, the solution was lyophilized to give a white solid. Recrystallization of the solid from water/acetonitrile yielded 380 mg of disodium 5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)-propionyl]phenyl phosphate as colourless needles of melting point 138° - 139°C.

Example 29

To a stirred solution of 380 mg of dibenzyl-phosphorochloridate in 10 ml of benzene was added a

solution containing 350 mg of 4-ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide, obtained as described in Example 12, and 51 mg of 60% sodium hydride in 10 ml of dimethylformamide. After stirring at room temperature for 14.5 hours, the mixture was diluted with 50 ml of ethyl acetate, washed three times with 50 ml of water each time, dried over sodium sulphate and evaporated to give 1.25 g of a yellow oil. The oil was chromatographed on 37.5 g of silica gel using ethyl acetate/hexane (1:1, v/v) for the elution. Removal of the solvent from the eluate gave 237 mg of dibenzyl 2-[(p-anisylamino)carbonyl]-5-ethoxy-3-methoxyphenyl phosphate as a colourless syrup which was dissolved in 20 ml of chloroform.

The solution obtained according to the preceding paragraph was hydrogenated for 34 hours in the presence of 47 mg of 10% palladium-on-charcoal at room temperature under atmospheric pressure. Removal of the catalyst by filtration followed by evaporation of the filtrate gave 94 mg of a white residue. Recrystallization of the

residue from methanol yielded 79 mg of 2-[(p-anisylamino)-carbonyl]-5-ethoxy-3-methoxyphenyl dihydrogen phosphate as colourless crystals of melting point 162° - 163.5°C.

The compound thus obtained was converted into disodium 2-[(p-anisylamino)carbonyl]-5-ethoxy-3-methoxyphenyl phosphate of melting point 126° - 127°C in a manner analogous to that described in Example 28.

Example 30

In a manner analogous to that described in Example 29, but using 2-hydroxy-4,6-dimethoxy-N-(p-methoxybenzyl)benzamide in place of 4-ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide, there was obtained 2-[(p-anisylamino)carbonyl]-3,5-dimethoxyphenyl dihydrogen phosphate as colourless crystals of melting point 160.5° - 162.5°C.

Example 31

To a stirred solution of 300 mg of 2-hydroxy-4,6-dimethoxy-N-(p-methoxybenzyl)benzamide, obtained as described in Example 7, and 50 mg of 60% sodium hydride in 3 ml of dimethylformamide were added 600 mg of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide. The mixture was stirred at room temperature for 18 hours and then treated with 50 ml of ethyl acetate and 30 ml of water. The ethyl acetate phase was separated, washed with water, dried over sodium sulphate and evaporated to give an oily residue. The residue was chromatographed on 10 g of silica gel using ethyl acetate for the elution. Removal of the solvent from the eluate followed by recrystallization from methanol gave 135 mg of 2-[(p-anisylamino)carbonyl]-3,5-dimethoxyphenyl tetra-O-acetyl-β-D-glucopyranoside as colourless crystals of melting point 73° - 76°C.

Example 32

To a suspension of 100 mg of 2-[(p-anisylamino)-carbonyl]-3,5-dimethoxyphenyl tetra-O-acetyl-β-D--glucopyranoside, obtained as described in Example 31, in 30 ml of methanol were added 0.09 ml of water and 0.09 ml of triethylamine. After stirring at room temperature for 3 days, the mixture was evaporated to give a solid residue. The residue was chromatographed on 10 g of silica gel using ethyl acetate/methanol (10:1, v/v) for the elution. Removal of the solvent from the eluate followed by recrystallization from ethanol/hexane yielded 40 mg of 2-[(p-anisylamino)-carbonyl]-3,5-dimethoxyphenyl β-D-glucopyranoside as colourless needles of melting point 132° - 133°C.

Example 33

To a stirred solution of 330 mg of 1-(4-ethoxy-2--hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone, obtained as described in Example 1, and 44 mg of 60%

sodium hydride in 5 ml of dimethylformamide was added tetra-O-acetyl-α-D-glucopyranosyl bromide. The mixture was stirred at room temperature for 18 hours, diluted with 30 ml of cold water and extracted with three 30 ml portions of ethyl acetate. The combined extracts were washed with water, dried over sodium sulphate and evaporated to give 700 mg of crude 5-ethoxy-3-methoxy--2-[3-(4-methoxyphenyl)propionyl]phenyl tetra-O-acetyl--β-D-glucopyranoside.

The foregoing crude material was purified by silica gel chromatography using hexane/ethyl acetate (3:1, v/v) for the elution and then saponified following the procedure described in Example 32 to give 5-ethoxy-3-methoxy-2-[3--(4-methoxyphenyl)propionyl]phenyl β-D-glucopyranoside; ^{1}H nmr: δ 1.35 (3H), 2.6 - 3.2 (4H), 3.2 - 4.6 (6H), 3.72 (3H), 3.78 (3H), 4.05 (2H), 4.87 (1H), 6.26 (1H), 6.45 (1H), 6.78 (2H) and 7.15 ppm (2H).

Example 34

In a manner analogous to that described in Example 12 but using 2'-hydroxy-6'-methoxy-4'-propoxyacetophenone in place of 4'-ethoxy-2'-hydroxy-6'-methoxyacetophenone, there was obtained 2-hydroxy-6-methoxy-4-propoxy-N-(p-methoxybenzyl) benzamide as colourless crystals of melting point 96.5° - 97.5°C (recrystallized from methanol).

Example 35

In a manner analogous to that described in Example 12 but using 2'-hydroxy-6'-methoxy-4'-(2-propenyloxy)acetophenone in place of 4'-ethoxy-2'-hydroxy-6'-methoxyacetophenone, there was obtained 4-(allyloxy)-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide as colourless crystals of melting point 69.5° - 70°C (recrystallized from methanol).

Example 36

In a manner analogous to that described in Example 12 but using 2'-hydroxy-6'-methoxy-4'-(3-methyl-2-butenyloxy) acetophenone in place of 4'-ethoxy-2'-hydroxy-6'-methoxyacetophenone, there was obtained 2-hydroxy-6-methoxy-4-(3-methyl-2-butenyloxy)-N-(p-methoxybenzyl)benzamide as colourless crystals of melting point 48.0° - 48.5°C (recrystallized from petroleum ether).

Example 37

In a manner analogous to that described in Example 29 but using 2-hydroxy-6-methoxy-4-propoxy-N-(p-methoxybenzyl) benzamide, obtained as described in Example 37, in place of 4-ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)benzamide, there was obtained disodium 2-[(p-anisylamino)carbonyl]-3-methoxy-5-propoxyphenyl phosphate as colourless crystals of melting point 116° - 119°C (recrystallized from ethyl acetate).

Example A

Tablets containing the following ingredients can be prepared by conventional procedures:

Active ingredient (i.e. a compound of formula I)	300 mg
Dried lactose	200 mg
Cellulose (microcrystalline)	30 mg
Polyvinylpyrrolidone	5 mg
Magnesium stearate	4 mg

Example B

Drops for intranasal administration containing the following ingredients per 1 ml can be prepared using methods known per se:

Active ingredient (i.e. a compound of formula I)	0.1 mg
Surfactant	0.05 mg
Propyleneglycol/water (1:1, v/v)	q.s. ad 1 ml

An acceptable range of concentration of the active ingredient is 0.001 to 1 mg/ml.

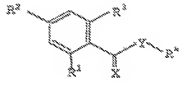
Example C

Trochés containing the following ingredients can be prepared using methods known per se:

Active ingredient (i.e. a compound of formula I)	0.1 g
Powdered sucrose	1.6 g
Acacia	0.2 g
Dextrin	0.1 g
Flavor	0.001 g

The embodiments of the invention in which an exclusive property or privilege is claimed, are defined as follows:

1) Process for the preparation of compounds of the general formula

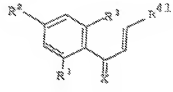


I

wherein X represents an oxygen or sulphur atom or hydroxyimino; Y represents methylene or imino; R^1 represents a hydroxy, phosphonooxy, glycosyloxy, acylated glycosyloxy, acyloxy or lower alkoxycarbonyloxy; R^2 represents lower alkoxy, lower alkenyloxy or lower alkylthio; R^3 represents lower alkoxy; R^4 represents lower alkyl, p-lower-alkoxybenzoyl or a phenyl, benzyl, pyridylmethyl, furfuryl, tetrahydrofurfuryl, thenyl tetrahydrothenyl, pyrrolylmethyl, pyrrolinylmethyl or pyrrolidinylmethyl group, with the proviso that when R^4 represents alkyl, a phenyl, benzyl or p-hydroxybenzyl, Y does not represent a methylene radical; and with the further proviso that when R^4 represents p-methoxybenzyl and Y represents methylene, R^2 and R^3 are different,

and pharmaceutically acceptable salts thereof, which process comprises

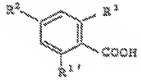
(a) hydrogenating a compound of the general formula



II

wherein X, R^1, R^2, R^3 are as defined in formula I, and R^{41} represents pyridyl, furyl, tetrahydrofuryl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl or pyrrolidinyl, in the presence of a catalyst in a solvent, or

(b) reacting a reactive derivative of a carboxylic acid of the general formula



III

wherein R^2 and R^3 are as defined in formula I and $R^{1'}$ represents a protected hydroxyl radical,

with a compound of the general formula

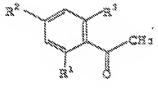
$$R^4 - NH_2 \qquad IV$$

wherein R^4 is as defined in formula I,

and then removing the protecting moiety of the protected hydroxyl radical,

or

(c) reacting an acetophenone of the general formula



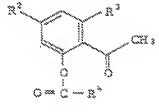
V

wherein R^1, R^2 and R^3 are as defined in formula I,

with iodine in a tertiary amine and reacting a resulting salt with an amine of formula IV given earlier in this claim,

or

(d) subjecting an ester of the general formula



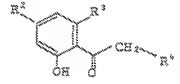
VI

wherein R^2, R^3 and R^4 are as defined in formula I,

to rearrangement in the presence of a base in a solvent,

or

(e) reacting a ketone of the general formula



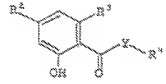
VII

wherein R^2, R^3 and R^4 are as defined in formula I,

with a salt of hydroxylamine in a solvent,

or

(f) reacting a carbonyl compound of the general formula



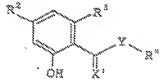
VIII

wherein Y, R^2, R^3 and R^4 are as defined in formula I,

with phosphorus pentasulphide in the presence of a base in a solvent,

or

(g) reacting a phenol of the general formula



IX

wherein Y, R^2, R^3 and R^4 are as defined in formula I and X' represents an oxygen or sulphur atom.

with an acylating agent in the presence of a base,

or

(h) reacting a phenol of formula IX given earlier in this claim with phosphorus oxychloride or dibenzyl-phosphorochloridate in the presence of a base in a solvent followed by hydrolysis or hydrogenolysis as the case may require and, if necessary, converting a resulting compound into a salt,

or

(i) reacting a phenol of formula IX given earlier in this claim with a glycosyl halide which may be acylated in the presence of a catalyst in a solvent, followed, if necessary, by the removal of the acyl radicals.

2) A process as in claim 1, wherein X represents an oxygen or sulphur atom or hydroxyimino; Y represents methylene or imino; R^1 represents a hydroxy, phosphonooxy, glycosyloxy, acylated glycosyloxy, acyloxy or lower alkoxycarbonyloxy; R^2 represents lower alkoxy, or lower alkylthio; R^3 represents lower alkoxy; R^4 represents lower alkyl, p-lower-alkoxy-benzoyl or a phenyl, benzyl, pyridylmethyl, furfuryl, tetrahydrofurfuryl, thenyl, tetrahydrothenyl, pyrrolylmethyl, pyrrolinylmethyl or pyrrolidinylmethyl group, with the proviso that when R^4 represents alkyl, phenyl, substituted phenyl, benzyl or p-hydroxybenzyl, Y does not represent a methylene radical; and with the further proviso that when R^4

represents p-methoxybenzyl and Y represents methylene, R^2 and R^3 are different.

3) A process as in claim 1, wherein R^1 is hydroxy, lower alkanoyloxy, benzoyloxy, phosphonooxy, lower alkoxycarbonyloxy; R^2 is lower alkoxy or lower alkenyloxy; R^3 is lower alkoxy; R^4 is lower alkoxy phenyl; and X is an oxygen or sulfur atom and Y is methylene or imino.

4) A process as in claim 1, wherein R^1 is hydroxy, lower alkanoyloxy, benzoyloxy, phosphonooxy, lower alkoxycarbonyloxy; R^2 is lower alkoxy or lower alkenyloxy; R^3 is lower alkoxy; R^4 is lower alkoxy phenyl; and X is an oxygen or sulfur atom and Y is imino.

5) A process as in claim 1 for the preparation of 4-ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl) benzamide, comprising reacting 4'-ethoxy-2'-hydroxy-6'-methoxy acetophenone with iodine in the presence of pyridine and reacting the resulting 1-[(4-ethoxy-2-hydroxy-6-methoxybenzoyl) methyl] pyridinium iodide with p-methoxybenzylamine.

6) A process as in claim 1 for the preparation of 2-[(p-anisylamino)carbonyl]-5-ethoxy-3-methoxyphenyl dihydrogen phosphate comprising hydrogenating dibenzyl 2-[(p-anisylamino)carbonyl] -5-ethoxy-3-methoxyphenyl phosphate.

7) A process as in claim 1 for the preparation of 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone comprising hydrogenating 4'-ethoxy-2'-hydroxy-4,6'-dimethoxychalcone.

8) A process as in claim 1 for the preparation of 5-ethoxy-3-methoxy-2-[3-(p-methoxyphenyl)-propionyl]phenyl acetate comprising reacting 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone with acetic anhydride.

9) A process as in claim 1 for the preparation of 2-hydroxy-4,6-dimethoxy-N-[p-(methylthio)benzyl]benzamide comprising reacting 2-(benzyloxy) -4,6-dimethoxybenzoic acid with p-(methylthio)-benzyl amine.

10) A process as in claim 1 for the preparation of 2-{[p-(allyloxy)benzyl]amino}carbonyl}-3,5-dimethoxyphenyl benzoate comprising reacting N-[p-(allyloxy)benzyl]-2-hydroxy-4,6-dimethoxybenzamide with benzoylchloride.

11) A process as in claim 1 for the preparation of 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanethione comprising reacting 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone with phosphorus pentasulphide.

12) A process as in claim 1 for the preparation of 5-ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)propionyl]phenyl ethyl carbonate comprising reacting 1-(4-ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone with ethoxycarbonyl chloride.

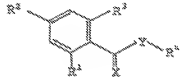
13) A process as in claim 1 for the preparation of 2-hydroxy-6-methoxy-4-propoxy-N-(p-methoxybenzyl)-benzamide comprising reacting 2'-hydroxy-6'-methoxy-4'-propoxyacetophenone with iodine in the presence of pyridine and treating the resulting pyridinium iodide with p-methoxybenzylamine.

14) A process as in claim 1 for the preparation of 4-(alloxy)-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)-benzamide comprising reacting 2'-hydroxy-6'-methoxy-4-(2-propenyloxy) acetophenone with iodine in the presence of pyridine and treating the resulting pyridinium iodide with p-methoxybenzylamine.

15) A process as in claim 1 for the preparation of 2-hydroxy-6-methoxy-4-(3-methyl-2-butenyloxy)-*N*-(p-methoxybenzyl)-benzamide comprising reacting 2'-hydroxy-6'-methoxy-4'-(3-methyl-2-butenyloxy) acetophenone with iodine in the presence of pyridine and treating the resulting pyridinium iodide with p-methoxy-benzylamine.

16) A process as in claim 1 for the preparation of disodium 2-[p-anisylamino)-carbonyl]-3-methoxy-5-propoxyphenyl phosphate comprising reacting 2-hydroxy-6-methoxy-4-propoxy-N-(p-methoxybenzyl) benzamide with dibenzylphosphorochloridate in the presence of sodium hydride.

17) Compounds of the general formula



I

wherein X represents an oxygen or sulphur atom or hydroxyimino; Y represents methylene or imino; R^1 represents a hydroxy, phosphonooxy, glycosyloxy, acylated glycosyloxy, acyloxy or lower alkoxycarbonyloxy; R^2 represents lower alkoxy, lower alkenyloxy or lower alkylthio; R^3 represents lower alkoxy; R^4 represents lower alkyl, p-lower-alkoxybenzoyl or a phenyl, benzyl, pyridylmethyl, furfuryl, tetrahydrofurfuryl, thenyl tetrahydrothenyl, pyrrolylmethyl, pyrrolinylmethyl or pyrrolidinylmethyl group, with the proviso that when R^4 represents alkyl, a phenyl, benzyl or p-hydroxybenzyl, Y does not represent a methylene radical; and with the further proviso that when R^4 represents p-methoxybenzyl and Y represents methylene, R^2 and R^3 are different, and pharmaceutically acceptable salts thereof, whenever prepared by the process claimed in claim 1 or by an obvious chemical equivalent thereof.

18) Compounds of formula I given in claim 18, wherein X represents an oxygen or sulphur atom or hydroxyimino; Y represents methylene or imino; R^1 represents a hydroxy, phosphonooxy, glycosyloxy, acylated glycosyloxy, acyloxy or lower alkoxycarbonyloxy; R^2 represents lower alkoxy, or lower alkylthio; R^3 represents lower alkoxy; R^4 represents lower alkyl, p-lower-alkoxy-benzoyl or a phenyl, benzyl, pyridylmethyl, furfuryl, tetrahydrofurfuryl, thenyl, tetrahydrothenyl, pyrrolylmethyl, pyrrolinylmethyl or pyrrolidinylmethyl group, with the proviso that when R^4 represents alkyl, a phenyl, benzyl or p-hydroxy-benzyl group, Y does not represent a methylene radical; and with the further proviso that when R^4 represents p-methoxy-benzyl and Y represents methylene, R^2 and R^3 are different, whenever prepared by the process claimed in claim 2 or by an obvious chemical equivalent thereof.

19) Compounds as in claim 18 wherein R^1 is hydroxy, lower alkanoyloxy, benzoyloxy, phosphonooxy, lower alkoxycarbonyloxy; R^2 is lower alkoxy or lower alkanyloxy; R^3 is lower alkoxy; R^4 is lower alkoxy phenyl; and X is a oxygen or sulfur atom and Y is methylene or imino, whenever prepared by the process claimed in claim 3 or by an obvious chemical equivalent thereof.

20) Compounds as in claim 18 wherein R^1 is hydroxy, lower alkanoyloxy, benzoyloxy, phosphonooxy, lower alkoxy-carbonyloxy; R^2 is lower alkoxy or lower alkanoyloxy; R^3 is lower alkoxy; R^4 is lower alkoxy phenyl; and X is a oxygen or sulfur atom and Y is imino, whenever prepared by the process claimed in claim 4 or by an obvious chemical equivalent thereof.

21) 4-Ethoxy-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)-benzamide, whenever prepared by the process claimed in claim 5 or by an obvious chemical equivalent thereof.

22) 2-[(p-Anisylamino)carbonyl]-5-ethoxy-3-methoxyphenyl dihydrogen phosphate and the disodium salt thereof, whenever prepared by the process claimed in claim 6 or by an obvious chemical equivalent thereof.

23) 1-(4-Ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanone, whenever prepared by the process claimed in claim 7 or by an obvious chemical equivalent thereof.

24) 5-Ethoxy-3-methoxy-2-[3-(p-methoxyphenyl)-propionyl]-phenyl acetate, whenever prepared by the process claimed in claim 8 or by an obvious chemical equivalent thereof.

25) 2-Hydroxy-4,6-dimethoxy-N-[p-(methylthio)benzyl]-benzamide, whenever prepared by the process claimed in claim 9 or by an obvious chemical equivalent thereof.

26) 2-{[[p-(Allyloxy)benzylamino]carbonyl}-3,5-dimethoxyphenyl benzoate, whenever prepared by the process claimed in claim 10 or by an obvious chemical equivalent thereof.

27) 1-(4-Ethoxy-2-hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)-1-propanethione, whenever prepared by the process claimed in claim 11 or by an obvious chemical equivalent thereof.

28) 5-Ethoxy-3-methoxy-2-[3-(4-methoxyphenyl)-propionyl]-phenyl ethyl carbonate, whenever prepared by the process claimed in claim 12 or by an obvious chemical equivalent thereof.

29) 2-Hydroxy-6-methoxy-4-propoxy-N-(p-methoxybenzyl)-benzamide, whenever prepared by the process claimed in claim 13 or by an obvious chemical equivalent thereof.

30) 4-(Allyloxy)-2-hydroxy-6-methoxy-N-(p-methoxybenzyl)-benzamide, whenever prepared by the process claimed in claim 14 or by an obvious chemical equivalent thereof.

31) 2-Hydroxy-6-methoxy-4-(3-methyl-2-butenyloxy)-N-(p-methoxybenzyl)-benzamide, whenever prepared by the process claimed in claim 15 or by an obvious chemical equivalent thereof.

32) Disodium 2-[p-anisylamino)-carbonyl]-3-methoxy-5-propoxyphenyl phosphate, whenever prepared by the process claimed in claim 16 or by an obvious chemical equivalent thereof.

*

SUBSTITUTE

REMPLACEMENT

there are NO DRAWINGS

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